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Escitalopram Causes Fewer Seizures in Human Overdose than Citalopram

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Abstract

Context: Seizures are a recognised complication of acute overdose with the racemic (1:1 ratio of R- and S-enantiomers) selective serotonin reuptake inhibitor antidepressant citalopram.

Objective: We tested the hypothesis that escitalopram (the therapeutically active S-enantiomer of citalopram) causes fewer seizures in overdose than citalopram at comparable doses of the S-enantiomer.

Methods: Multicentre retrospective review of cases with citalopram and escitalopram overdose reported to German, Austrian and Swiss Poisons Centres between 1997-2006.

Results: 316 citalopram and 63 escitalopram cases were analysed. Somnolence, nausea, vomiting, tachycardia, QT-prolongation and tremor occurred with similar frequency in both groups. There was a striking difference in the frequency of single and multiple seizures: 43 cases (13.5%) in the citalopram group, 1 case (1.6%) with a single seizure in the escitalopram group (p=0.0065).

Discussion and conclusions: At comparable ingested doses of the S-enantiomer the symptom profile for citalopram and escitalopram intoxications is similar except for seizures which occur more frequently in citalopram than in escitalopram poisoning.

Introduction

Citalopram (1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro[2]benzofuran-5-carbonitrile) is a selective serotonin reuptake inhibitor (SSRI) which was introduced in 1991 for the treatment of depression, panic disorders and obsessive-compulsive disorder (Ref: Product Information). Citalopram consists of a 1:1 racemic mixture of the *S*-(+)- and *R*-(-)-enantiomers and the therapeutic dosage is usually 20-60 mg/day. In comparison with citalopram the inhibition of serotonin reuptake is twice as high for escitalopram (the therapeutically active S-enantiomer) which was introduced in 2001.[1] Accordingly, the therapeutic dose of escitalopram is approximately half the dose of citalopram, usually 10-20 mg/day. Studies comparing the therapeutic effect in major depressive disorder have suggested that escitalopram at an equipotent dose (20 mg/day) may have some clinical benefits over citalopram at full dose (40 mg/day), such as a better MADRS score decrease (Montgomery-Asberg Depression Rating Scale),[2] and lower drop-outs.[3]

Information on overdoses with citalopram and escitalopram is limited. Seizures, ECG changes such as prolonged QT intervals and sinus tachycardia have been described in studies with citalopram overdose.[4,5,6] In contrast, a study with 28 cases involving accidental or intentional overdose of escitalopram found that no patient developed adverse sequelae.[7] In another study the most frequent symptoms were neurological (drowsiness, dizziness, agitation and tremor), followed by gastrointestinal (vomiting and nausea) and cardiovascular (tachycardia).[8] Ho et al.[9] described seizures and QT prolongation as the most serious symptoms with citalopram and escitalopram overdose.

Since seizures and ECG changes have been observed at doses of ≥600 mg in citalopram overdose[5] one would expect a similar profile of symptoms in escitalopram overdose at a dose of around 300 mg under the assumption that the therapeutically active enantiomer is responsible for these effects. However, a recent paper suggested that seizures are more common in citalopram than escitalopram overdose.[10] This observation is consistent with anecdotal evidence from escitalopram overdoses reported to the Swiss Toxicological Information Centre where no seizures

were recorded. We therefore designed a multicentric study to evaluate the profile of symptoms in escitalopram and citalopram overdose and to test the hypothesis that escitalopram causes fewer seizures in overdose than citalopram at comparable doses of the S-enantiomer.

Methods

The study was designed as a multicentre retrospective review of cases with citalopram and escitalopram overdose reported between January 1997 and December 2006 to Poisons Centres in Germany (Berlin, Bonn, Erfurt, Freiburg, Mainz, Munich, Göttingen), Austria (Vienna) and Switzerland (Zurich). The centres were asked to provide the anonymised data in a standardised[11] exchange spread sheet format. Data (age, sex, ingested drug and dose, symptoms, causality, decontamination measures, latency to decontamination and outcome) were entered by physicians blinded to the hypothesis of the present study. All cases were reviewed by a physician at the Swiss Toxicological Information Centre (STIC) before they were entered into the study to ensure that they met the inclusion criteria. Since not all centres classify severity of symptoms in the same way the cases were also re-evaluated according to the Poisoning Severity Score (PSS) developed by the European Association of Poison Centres and Clinical Toxicologists, the International Programme on Chemical Safety and the European Commission.[12]

Inclusion criteria

The following criteria had to be met for reported cases to be included in the study:

- Monointoxication with either citalopram or escitalopram;
- follow up, reported by the treating physician, for an observation period of at least 6 hours after the ingestion;
- patient age ≥ 16 yr;
- ingested dose known within a limit of +/- 10%;
- a likely causal relationship between overdose and clinical effect. This assessment was based on a clear temporal relationship between drug ingestion and intoxication symptoms, absence of other drugs or diseases that

could explain the symptoms, and a transitory nature of the symptoms. Since these criteria could not be used for asymptomatic patients, these cases were judged according to the ingestion dose reported by the patient or by relatives.

Data classification

According to the PSS, the severity of symptoms of individual patients was classified as ‘minor’ if only minor symptoms were present, as ‘moderate’ if at least one moderate symptom developed, and as ‘severe’ if at least one severe symptom was observed. A summary of symptoms according to their severity is shown in Table 1.

Statistical evaluation

The statistical evaluation was performed with StatView (SAS Institute Inc. Cary N. C., Version 5.0.1). The doses of citalopram (S-enantiomer) and escitalopram were compared using the unpaired Student's t-test. Chi-square analysis was used to test for frequency of symptoms. A $p<0.05$ (two-way) was considered statistically significant.

Results

During the study period (January 1997-December 2006) a total of 316 cases with citalopram monointoxication and 63 escitalopram monointoxications that fulfilled all inclusion criteria were reported from the following centres: Berlin (13 cases with citalopram/1 case with escitalopram), Bonn (22/4), Erfurt (24/3), Freiburg (40/2), Göttingen (3/-), Mainz (84/8), Munich (5/1), Vienna (-/16) and Zurich (125/28).

The demographic characteristics of patients in the citalopram and escitalopram groups were similar with both groups showing a predominance of females and a mean age of just over 30 years (Table 2). The ingested citalopram doses ranged from 80 mg to 4200 mg (mean 712 mg corresponding to 356 mg of the S-enantiomer). For escitalopram, the dose range was 40 mg to 1860 mg (mean 322 mg). There was no significant difference between ingested doses of the S-

enantiomer in the citalopram and escitalopram group (p=0.49), both overall and in the individual severity categories. In both groups the severity of symptoms was related to the ingested dose (Table 3). However, the distribution of cases within the severity categories was different between the two groups, with escitalopram showing proportionally more asymptomatic cases, and no cases with severe symptoms.

The reported symptoms and their severity classification are shown in Table 4. Somnolence was by far the most frequently reported symptom for both citalopram and escitalopram intoxications (43.7% and 40.0%, respectively). Other common symptoms such as nausea and vomiting, tachycardia, QT-prolongation and tremor also occurred with similar frequency in both groups. However, there was a striking difference in the frequency of single and multiple seizures: 43 cases (14%) were seen in the citalopram group and only 1 case (2%) with a single seizure was reported in the escitalopram group (Table 5). Accordingly, seizures were the most frequent symptom determining moderate (48.5% of symptoms) and severe outcomes (83.3% of symptoms) in the citalopram group, but not the escitalopram group (10.0% of moderate symptoms and no severe outcomes).

The dose range in which seizures were seen was 280-4200 mg (mean 1568 mg, corresponding to 784 mg of S-enantiomer) for citalopram versus 1860 mg for the single escitalopram case. In the citalopram group the lowest dose at which a seizure occurred was 140 mg S-enantiomer (280 mg citalopram) followed by 2 cases with 200 mg S-enantiomer (400 mg citalopram). Overall in the citalopram group seizures were seen at doses of 200-400 mg S-enantiomer in 8 of 73 cases (11%); at doses of 401-600 mg S-enantiomer in 11 of 41 cases (27%); at doses of 601-800 mg S-enantiomer in 7 of 17 cases (41%) and in the higher dose range (>800 mg) in 14 of 27 cases (52%).

Gastric lavage and activated charcoal were used for gastrointestinal decontamination. In 37 (11.7 %) patients with citalopram overdose and in 6 (9.5%) patients with escitalopram overdose gastrointestinal decontamination was performed within one hour. In 149 (47.2 %) citalopram and 21 (33.3 %) escitalopram cases no decontamination was performed or it was performed later than 1h after ingestion. In

130 (41.1%) cases with citalopram ingestion and in 36 (57.2 %) cases with escitalopram ingestion no information on decontamination was provided (Table 2).

Discussion

This study compares the clinical symptoms and dose response relationship in 316 patients with citalopram and 63 patients with escitalopram overdose. It was designed to test the hypothesis that escitalopram causes fewer seizures in overdose than citalopram at comparable doses of the S-enantiomer.

The demographic characteristics of patients in the citalopram and escitalopram groups were similar. There was no significant difference between ingested doses of the S-enantiomer in the citalopram and escitalopram groups. The fact that the frequency of somnolence, vomiting, tachycardia, QT-prolongation and tremor was similar in the citalopram and escitalopram groups would also suggest that the ingested doses were of similar potency in terms of overall toxicity profile. However, we found a striking difference in the frequency of seizures with 14% in the citalopram group versus 2% in the escitalopram group. Despite the difference in group size this result was statistically significant.

The symptoms of citalopram overdose in our study were similar to those described in the literature. Seizures, prolonged QT intervals and sinus tachycardia have been described in a study with five patients who took up to 5200 mg of citalopram.[4] A review of 44 patients with citalopram overdose ≥ 600 mg showed seizures and ECG changes.[5] In this study the frequency of patients developing seizures was 14%, an almost identical result to our investigation.

Information in the literature on symptoms following escitalopram overdose is very limited. Lo Vecchio et al.[7] found no seizures in a retrospective chart review of 28 patients with escitalopram overdose. In another study[8] with 1179 cases of escitalopram ingestion the most frequently observed adverse effects were neurological (drowsiness, dizziness, agitation and tremor), followed by gastrointestinal (vomiting and nausea) and cardiovascular (tachycardia). Seizures

were observed in 3 cases (0.3%). Van Gorp et al.[13] describe serotonin toxicity, QT prolongation and bradycardia as major manifestations of escitalopram overdose. No seizures were observed in this study including 79 patients.
Recently the first study comparing the toxicity of citalopram versus escitalopram in overdose was published.[10] Most frequently reported clinical effects with citalopram and escitalopram were tachycardia, drowsiness, hypertension, and vomiting. Seizures (8% vs. 0.2%, respectively) and tremor (8.6% vs. 3.1%, respectively) were more common with citalopram. In a congress presentation of a study with 228 patients with citalopram and 33 patients with escitalopram overdose, seizures and QT prolongation were the most serious symptoms. In this study 17 cases (7.5%) with seizures were seen in the citalopram group and 1 case (3%) in the escitalopram group.[9]

The lowest dose that caused seizures in our citalopram case series was 280 mg (corresponding to 140 mg S-enantiomer). There is little information in the literature concerning a dose response for seizures in overdose. Two authors mention 400 mg[10,14] and two authors 600 mg or more[4,5] as the minimal dose for seizures. The difference between these doses and that seen in our study may be related to the smaller number of cases compared to our study.
The only patient developing seizures in our study ingested 1860 mg escitalopram, which is considerably higher than the 300 mg described in the single case of seizures observed by Hayes et al.[10]

Our study was not designed to investigate the reasons for the difference of the two substances with regard to the development of seizures in overdose. Seizures are caused by an imbalance between excitatory and inhibitory influences. Thus, epileptogenesis can arise if excitatory transmission is facilitated or inhibitory transmission is reduced. $GABA_B$ receptors, serotonin receptors and histamine H_1 receptors have all been reported to have some role in this process.[15,16,17,18] However, data for citalopram and escitalopram suggest that there is no difference in receptor affinity for serotonin and $GABA_B$ in comparable doses of the S-enantiomer. With regard to serotonin reuptake transporter (SERT) occupancy, Klein et al.[19] reported no significant difference when comparing administration of an equivalent single dose of escitalopram and the S-enantiomer of citalopram. However, a higher SERT

occupancy in midbrain was found after multiple dose administration of 10 mg/day escitalopram compared to 20 mg/day citalopram. These results may be explained by an attenuating effect of R-citalopram on the occupancy of S-citalopram at the serotonin transporters.[20] Hyttel and Sanchez found no difference in $GABA_B$ receptor affinity between R- and S-enantiomer.[1,21] However, the fact that the R-enantiomer of citalopram has some affinity for H_1 receptors suggests the possibility of a lowering of inhibitory influences over histamine receptors.[1] Among other neurotransmitters, histamine has been described to have a role in the inhibition of seizures via H_1 histamine receptors.[18] Thus, the H_1 antagonistic effect of the R-enantiomer could possibly impair anticonvulsant activity.

Apart from serotonin, histamine and $GABA_B$ receptors there are other possible mechanisms for seizures. However, Jobe[22] showed that noradrenergic influences do not account for the proconvulsant properties of antidepressant drugs.
The glycine receptor (GlyR) is one of the major inhibitory receptors in the adult mammalian central nervous system. Inhibition at the glycine receptor might play a significant role in SSRI-associated seizures,[23] but no information in the literature could be found regarding the affinity of the R- and S-citalopram enantiomers for this receptor.

G protein-activated inwardly rectifying K^+ (GIRK) channels also play an important role in the inhibitory regulation of neuronal excitability in most brain regions through activation of various G protein coupled receptors.[24] It has been suggested that the inhibition of neuronal GIRK channels may contribute to the occurrence of seizures in overdose with citalopram.[25] However, there is no comparative study on inhibition of GIRK channels by R- and S-citalopram.

Interpretation of our findings is limited by the retrospective nature of the study design. In addition, our strict inclusion/exclusion criteria, in particular the decision to only include monointoxications and cases with a known ingested dose led to small case numbers especially in the escitalopram group. However, we felt that these restrictions were necessary in order to be able to interpret the findings, in particular since we were not able to obtain confirmation of the ingested dose by measuring serum concentrations of citalopram and escitalopram. Comparing the dose of escitalopram

with that of the racemic mixture citalopram is hampered by the lack of information on the clinical effect of the R-enantiomer. However, for the reasons stated above and from a clinician's point of view we believe it is justified to compare the therapeutically active moieties rather than the amount of chemical substance.

Conclusions

In conclusion, our findings add substantial weight to previous suggestions that citalopram is more likely to cause seizures than escitalopram in overdose at comparable doses of the S-enantiomer. The reasons for this difference are currently unclear but may be related to a lowering of inhibitory influences on histamine receptors by the R-enantiomer of citalopram. This may make escitalopram a safer drug in overdose, but it is important to confirm our findings in a prospective study, and to investigate the possible mechanisms for this difference.

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Declaration of interest

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Table 1. Symptoms and severity of intoxication

	Minor	**Moderate**	**Severe**
Nervous system	Somnolence, dizziness, tremor, restlessness, drowsiness, tinnitus, ataxia, mild anticholinergic symptoms (dry mouth, mydriasis)	Unconsciousness with appropriate response to pain (GCS* 8-9), agitation, single generalized or local seizures, myoclonia	Deep coma with inappropriate response to pain or unresponsive to pain (GCS ≤7), multiple generalized seizures
Cardiovascular system	Mild ECG changes (QTc† >390ms ♂, >440ms ♀; extra systoles, right bundle branch block) Tachycardia (100-139 bpm)	Moderate ECG changes (QTc >430ms ♂, >485ms ♀; AV block I°) Tachycardia (140-179 bpm)	
Gastrointestinal tract	Vomiting, nausea, diarrhea, pain	Pronounced or prolonged vomiting, diarrhea, pain, ileus, intestinal atonia	

*Glasgow Coma Scale; †QT interval corrected for heart rate.

Table 2. Patient baseline characteristics

	Citalopram	**Escitalopram**
Number of patients	316	63
Sex female:male:unknown (%)	74:19:7	68:27:5
Age (years)		
- mean ± SD	31.5 ± 14.8	32.4 ± 13.1
- median, range	30.0, 16-84	32.5, 16-60
Dose (mg)		
- mean	712	322
- range	80-4200	40-1860
- S-enantiomer	356	322 (p=0.49)
Decontamination		
- within 1h	37 (11.7%)	6 (9.5%)
- >1h/no decontamination	149 (47.2%)	21 (33.3%)
- unknown	130 (41.1%)	36 (57.2%)

Table 3. Severity of symptoms and ingested dose

	Citalopram (n=316)		Escitalopram (n=63)	
	Number of cases	**Dose** (mg) Range, mean, mean of S-enantiomer	**Number of cases**	**Dose** (mg) Range, mean
No symptoms	53 (17%)	80-2000, 423, 211	20 (32%)	60-400, 223
Minor	199 (63%)	80-3920, 565, 282	35 (55%)	40-1200, 318
Moderate	50 (16%)	100-4200, 1307, 653	8 (13%)	60-1860, 588
Severe	14 (4%)	200-4000, 1788, 894		

Table 4. Clinical effects

	Citalopram N= 316			Escitalopram N= 63		
	Minor	Moderate	Severe	Minor	Moderate	Severe
Somnolence	138 (43.7%)			25 (40 %)		
Coma - moderate (GCS* 8-9)		6 (1.9%)			1 (1.6%)	
- severe (GCS ≤ 7)			2 (0.6%)			
Dizziness	25 (7.9%)			2 (3.1%)		
Restlessness	11 (3.5%)			2 (3.1%)		
Agitation		13 (4.1%)			4 (6.3%)	
Hallucination		3 (0.9%)				
Convulsion - simple		33 (10.4%)			1 (1.6%)	
- multiple			10 (3.1%)			
Other Symptoms of the nervous system (hyperreflexia, apathy, slow down, amnesia, speech disorder, ataxia, paraesthesia)	11 (3.5%)					
Myclonia		8 (2.5%)				
Tremor	26 (8.2%)			8 (12.7%)		
Mydriasis	21 (6.6%)			3 (4.7%)		
Tachycardia - (100-139 bpm)	53 (16.8%)			7 (11.1%)		
- (140-179 bpm)		1 (0.3%)				
ECG changes - mild (QTc >390ms ♂, >440ms ♀, extra systoles, right bundle branch block)	25 (7.9%)			4 (6.3%)		
- moderate (QTc >430ms ♂, >485ms ♀)		2 (0.6%)			1 (1.6%)	
AV-Block I°		2 (0.6%)				
Nausea	32 (10.1%)			4 (6.3%)		
Vomiting	56 (17.7%)			8 (12.7%)		
Vomiting prolonged					1 (1.6%)	
Intestinal atonia					1 (1.6%)	
Urinary retention					1 (1.6%)	

*Glasgow Coma Scale.

Table 5. Most frequent symptoms

	Citalopram (n=316)		**Escitalopram (n=63)**		p
Somnolence	138	(44%)	25	(40%)	0.56
Vomiting	56	(18%)	9	(14%)	0.51
Tachycardia	54	(17%)	7	(11%)	0.24
Seizures	43	(14%)	1	(2%)	0.0065
QT-prolongation	27	(9%)	5	(8%)	0.87
Tremor	26	(8%)	8	(13%)	0.25

P values for the comparison between the two groups of the most frequent symptoms are calculated using Chi-square analysis. A $p<0.05$ (two-way) was considered statistically significant.